

Efficacy and Safety of Probuphine for the Maintenance Treatment of Opioid Dependence in Clinically Stable Patients

NDA 204442

Probuphine (buprenorphine hydrochloride) Implant

FDA Presentation

**Psychopharmacologic Drugs
Advisory Committee (PDAC) Meeting
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Outline

- **Background**

- Buprenorphine Transmucosal Formulations
- Probuphine
- Regulatory History

- **Efficacy**

- PRO-814

- **Safety**

- Rods and Insertion/Removal Procedures

Background: Buprenorphine

Drug Substance Properties	
Class	<ul style="list-style-type: none">• Partial μ-opioid receptor agonist
Indication	<ul style="list-style-type: none">• Treatment of opioid dependence<ul style="list-style-type: none">• Typical maintenance dose 16 mg (16/4) in Subutex (Suboxone) tablet equivalents for new entrants to treatment
Dose-dependent Activity	<ul style="list-style-type: none">• At lower doses, can ameliorate withdrawal symptoms• At sufficiently high doses, provides opioid blockade
Safety and Tolerability	<ul style="list-style-type: none">• Withdrawal syndrome delayed and reduced in intensity• Ceiling effect – plateau of agonist effects

Transmucosal Formulations Used in Opioid Dependence Treatment

Transmucosal Formulation	Year Approved
Suboxone and Subutex Sublingual Tablet formulations <ul style="list-style-type: none"> • (no longer marketed; generics available) 	2002
Suboxone Sublingual Film <ul style="list-style-type: none"> • Buccal administration – 2015 	2010
Zubsolv Sublingual Tablet	2013
Bunavail Buccal Film	2014

Transmucosal Buprenorphine Formulations: Corresponding Doses

		Corresponding doses of buprenorphine products that contain naloxone			
Product Name	Subutex sublingual tablets, including generic equivalents	Suboxone sublingual tablets, including generic equivalents	Suboxone sublingual films	Zubsolv sublingual tablets	Bunavail buccal films
Dose Strengths Available	2 mg buprenorphine	2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone	1 mg buprenorphine/ 0.2 mg naloxone
			4 mg buprenorphine/ 1 mg naloxone	2.9 mg buprenorphine/ 0.71 mg naloxone	2.1 mg buprenorphine/ 0.3 mg naloxone
		8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone	4.2 mg buprenorphine/ 0.7 mg naloxone
			12 mg buprenorphine/ 3 mg naloxone	8.6 mg buprenorphine/ 2.1 mg naloxone	6.3 mg buprenorphine/ 1 mg naloxone
				11.4 mg buprenorphine/ 2.9 mg naloxone	
Route of Administration	Sublingual	Sublingual	Sublingual Buccal	Sublingual	Buccal

Drug Utilization Data

- **Patients:**

- In 2014, 1.3 million patients received dispensed prescriptions for oral transmucosal buprenorphine-containing products from U.S. outpatient retail pharmacies

- **Top Prescribers:**

	Year 2014	
	TRxs (N)	Share (%)
Total Prescriptions	10,634,561	100.0%
GP/FP/DO*	4,053,488	38.1%
Psychiatry	2,498,200	23.5%
Internal Medicine	1,681,452	15.8%
Anesthesiology	426,069	4.0%
Emergency Medicine	361,240	3.4%
All Other Specialties	1,614,112	15.2%

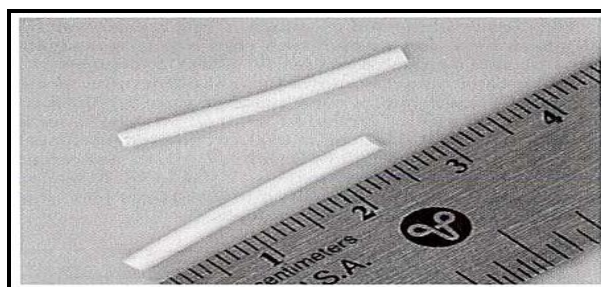
*GP/FP/DO: General Practice/Family Practice/Osteopathic Medicine

Nationally Estimated Number of Prescriptions Dispensed for Oral Transmucosal Buprenorphine Containing Products from U.S. Outpatient Retail Pharmacies, by Prescriber Specialties

Background: Probuphine

(buprenorphine; ethylene vinyl acetate)

- Product/Class: Implantable formulation of buprenorphine (BPN)
 - Properties of Individual Rods
 - 80 mg BPN & ethylene vinyl acetate
 - 26 mm long x 2.5 mm diameter rods
 - Sustained release of BPN for up to 6 months



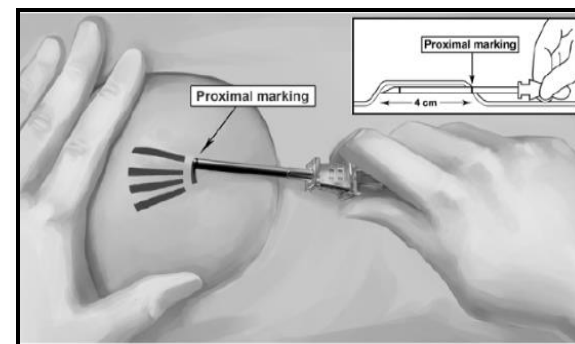
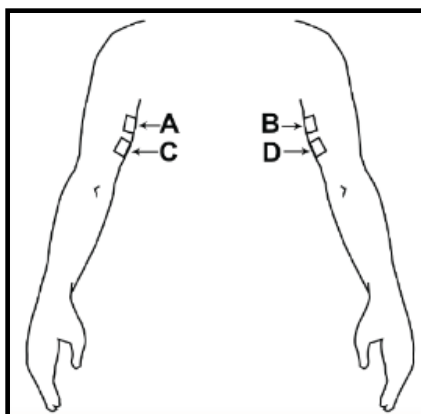
- Applicant's Proposed Indication: “for the maintenance treatment of opioid dependence and should be used as part of a complete treatment program to include counseling and psychosocial support.”

Background: Probuphine

(buprenorphine; ethylene vinyl acetate)

- Dosage/Administration:

- Population: “should be used only in patients who are opioid tolerant and are currently on a maintenance dose of 8 mg or less of sublingual Subutex or Suboxone equivalent.”
- Insertion/Removal/Continuation: 4 rods inserted into inner upper arm for 6 months
 - No experience with insertion/removal beyond 2 administration sites (L & R arm)



Regulatory History

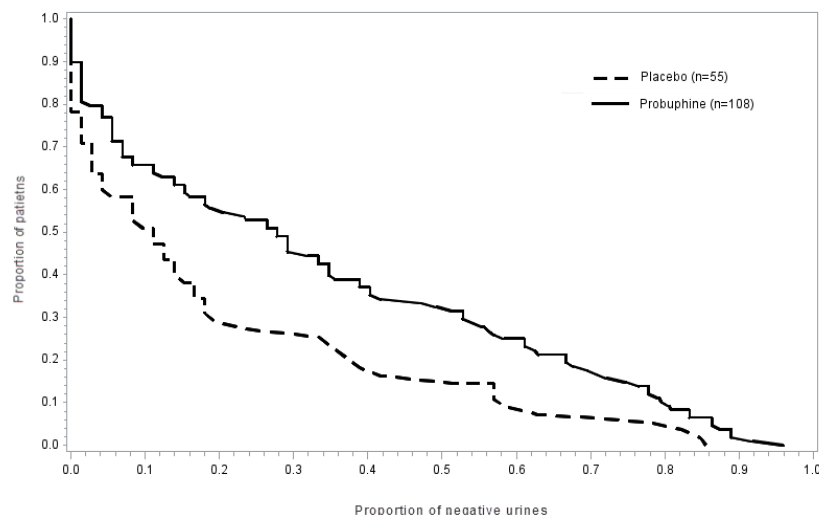
- **Initial NDA Submission – October 31, 2012**
 - 505(b)(2) relying on Agency safety and efficacy findings for Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone) tablets
 - Previous Indication Proposed: Maintenance treatment of opioid dependence
 - 4 – 5 rods/implants for 6 months, per 6-month treatment cycle
 - initial insertion following target dose of 12–16 mg sublingual (SL) BPN for 3 consecutive days (target dose reached in 10–16 days)
 - Clinical Development Program
 - PRO-805 & PRO-806 – Two 6-month safety and efficacy trials
 - 2 six-month extension studies (PRO-807 & PRO-811)
 - PK study
 - BA study (SL BPN 16 mg)

Regulatory History

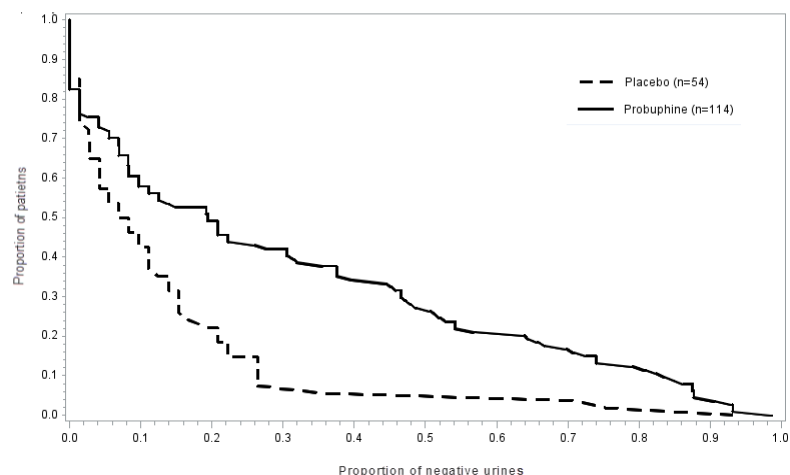
- **Initial NDA Submission – October 31, 2012**
 - Probuphine Clinical Trials – PRO-805 & PRO-806
 - Two 6-month safety and efficacy trials
 - New entrants to treatment received 4 Probuphine or 4 placebo implants, option for 5th rod
 - Rescue BPN permitted
 - Used in treatment failure definition and as withdrawal criterion
 - Not a factor in determining treatment response
 - Efficacy based on urine toxicology and self-report
 - Urine samples collected 3x/week
 - Investigators blinded to urine toxicology results
 - Cumulative Distribution Function (CDF) of % opioid(-) urines over 6 months
 - Missing urines positive – missed visits or discontinuations

Primary Efficacy Results, Weeks 1 – 24

CDF % (-) urines, PRO-805



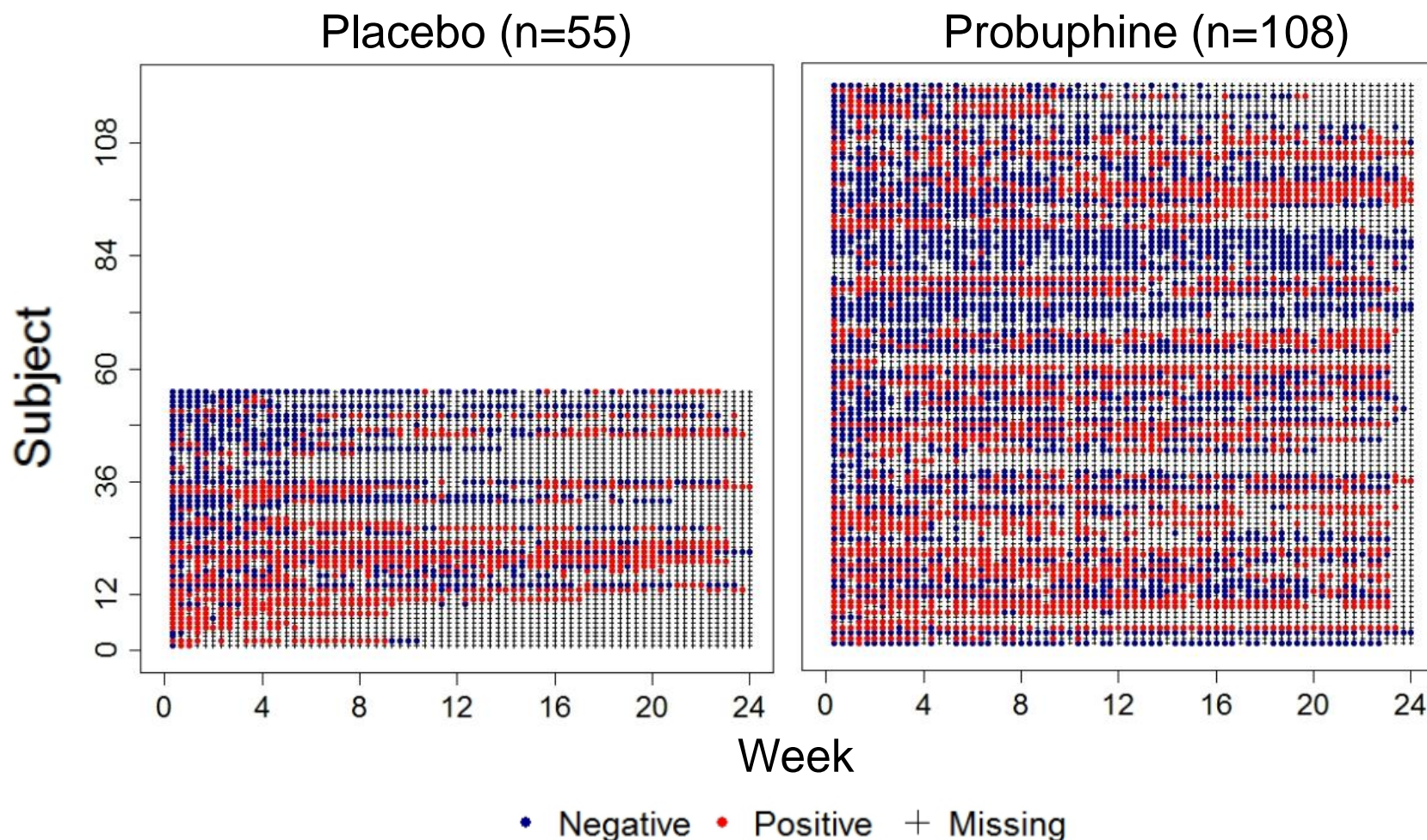
CDF % (-) urines, PRO-806



% (-) urines Weeks 1 – 24			
Study	% (-) urines	% of subjects	
		Probuphine	Placebo
PRO-805	≥ 30	45	27
	≥ 50	32	16
	≥ 75	15	7
	≥ 80	10	5
	≥ 85	6	2
	≥ 90	2	-
	≥ 95	1	-
	100	-	-
PRO-806	≥ 30	42	7
	≥ 50	27	6
	≥ 75	13	4
	≥ 80	12	2
	≥ 85	9	2
	≥ 90	4	2
	≥ 95	1	-
	100	-	-

Study PRO-805

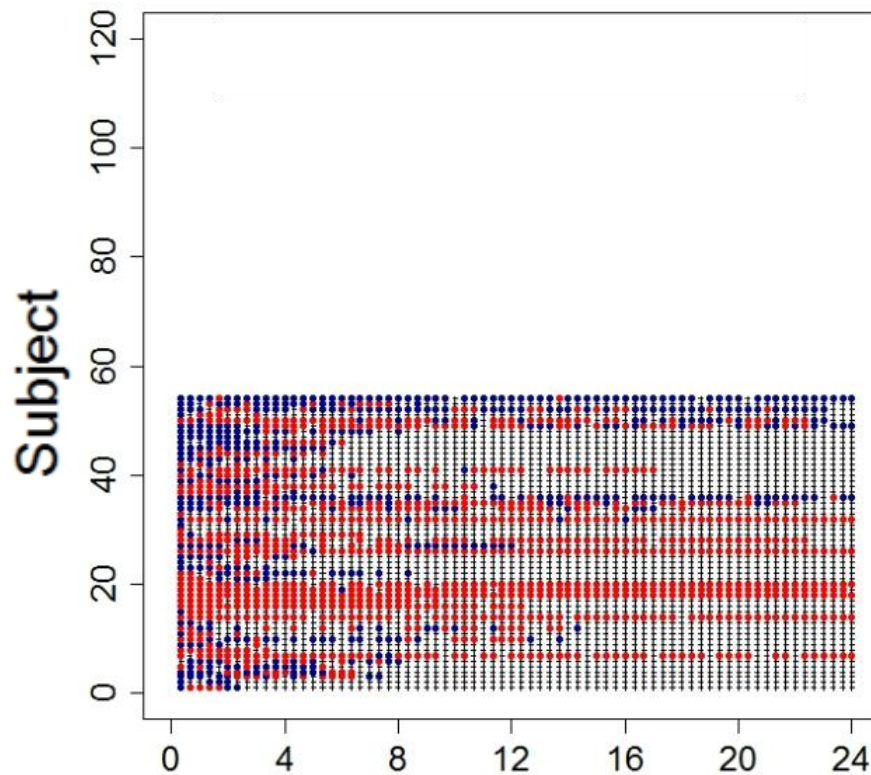
Subject-level results of urine samples



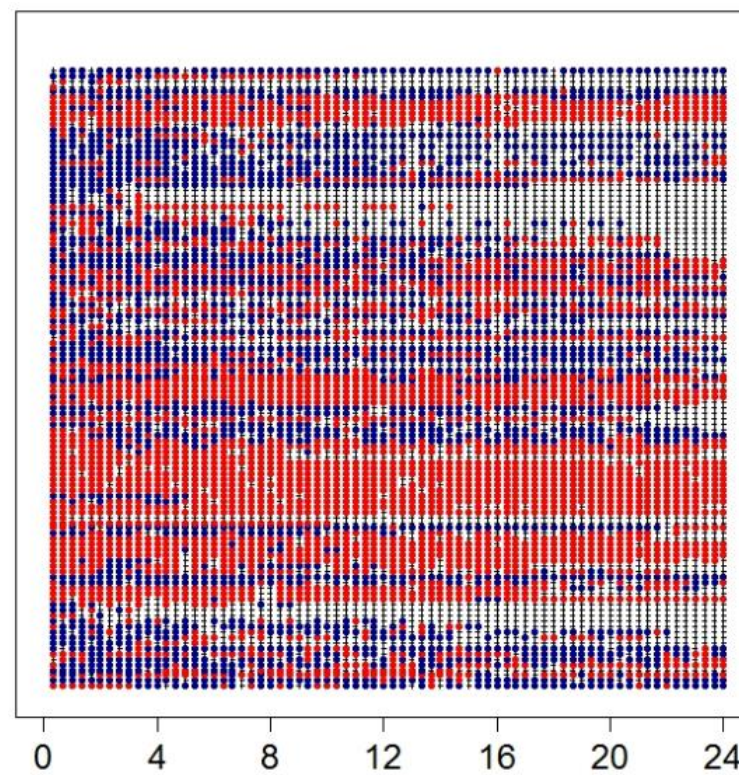
Study PRO-806

Subject-level results of urine samples

Placebo (n=54)



Probuphine (n=114)



Week

• Negative • Positive + Missing

Regulatory History

- **Summary of Review Findings for Initial October 2012, Submission**
 - Efficacy – Appropriateness of Dose
 - Buprenorphine plasma levels with Probuphine
 - 0.9 ng/ml treat withdrawal symptoms vs. ~3 ng/mL for blockade
 - Implant safety
- **AC Meeting – March 21, 2013**
 - Safety concerns with procedures for insertion/removal; Efficacy; Risk Evaluation and Mitigation Strategy (REMS)
- **Complete Response Letter – April 30, 2013**
 - Clinical benefit of minor changes in drug-taking behavior not established
 - Opioid blockade study
 - Higher doses of Probuphine
 - Insertion and Removal Procedures / Training Program not validated
 - Human factors evaluation

Regulatory History

- **Post-Action Meeting – November 19, 2013**
 - Applicant proposed limiting Probuphine's indication to patients stabilized on SL BPN ≤ 8 mg
 - Probuphine plasma exposure levels \approx SL BPN 8 mg/day
 - Novel population, indication, and study design; standardized clinical stability definition
 - Flexibility deemed appropriate in light of public health issue
 - A limited indication could be considered, but trial would be needed
- **Series of Post-Meeting Communications to discuss PRO-814**
 - Study design for limited indication

Probuphine NDA Resubmission

PRO-814

PRO-814 Trial

Design	Phase 3, Multicenter, Double-Blind, Double-Dummy, Active Control (SL BPN), Efficacy and Safety Trial <ul style="list-style-type: none">21 US sites
Subjects	Adults with opioid dependence diagnosis <ul style="list-style-type: none">Stable per healthcare provider (HCP), confirmed by:<ul style="list-style-type: none">On SL BPN treatment x 6 months (≥ 24 weeks)<ul style="list-style-type: none"><i>previous 6 months intended; cumulative lifetime total used</i>On SL BPN ≤ 8 mg/day \leq last 90 days<ul style="list-style-type: none"><i>Subutex and Suboxone tablet equivalents</i>\bigcirc opioid (+) urine toxicology last 90 daysClinical Stability Checklist<ul style="list-style-type: none">HCP confirmation of clinical stability

Clinical Stability Checklist



PRO-814 Checklist for Clinical Stability

A potential study subject must be considered clinically stable by their treating healthcare provider and confirmed by the following attestation:

Patient Name _____

Treating Physician Name _____

Treating Physician Address _____

I consider this patient clinically stable based on the following (please check all that apply)

- a. Patient has not reported any illicit opioid drug use in the past 90 days _____
- b. Patient has a stable living environment _____
- c. Patient participates in a structured activity/job that contributes to the community _____
- d. Patient has not reported significant withdrawal symptoms in the past 90 days _____
- e. Patient has consistently participated in recommended cognitive behavioral therapy/peer support program _____
- f. Patient has been consistently compliant with clinic visit requirements _____
- g. Patient has reported low to no desire/need to use illicit opioids in the past 90 days _____
- h. No episodes of hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions in the previous 90 days
- i. Please describe any other indicators of clinical stability that you have observed _____

Treating Physician Signature _____

Source: PRO-814 Manual of Procedures

Clinical Stability Checklist

I consider this patient clinically stable based on the following (please check all that apply)

- Patient **has not reported any illicit opioid drug use** in the past 90 days_____
- Patient has a **stable living environment**_____
- Patient participates in a **structured activity/job** that contributes to the community_____
- Patient has not reported **significant withdrawal symptoms** in the past 90 days_____
- Patient has consistently participated in recommended **cognitive behavioral therapy/peer support program**_____
- Patient has been consistently **compliant with clinic visit requirements**_____
- Patient has reported **low to no desire/need to use illicit opioids** in the past 90 days_____
- No episodes of **hospitalizations** (addiction or mental health issues), **emergency room visits**, or **crisis interventions** in the previous 90 days
- Please describe any **other indicators** of clinical stability that you have observed

PRO-814 Trial

Treatments	<ul style="list-style-type: none">• Group A: <u>SL BPN \leq 8 mg/day</u> + 4 Placebo Implants• Group B: <u>4 Probuphine Implants</u> + SL Placebo• Supplemental SL BPN permitted <i>Subjects were told that while additional counseling and other pharmacological interventions were available, their then-current dose of BPN was expected to be adequate to maintain stability and that they were not expected to need supplemental SL BPN.</i> Sporadic use, if any, anticipated, and therefore, supplemental use not factored into response definitions.
Assessments	<ul style="list-style-type: none">• 6 scheduled + 4 random urine toxicology visits• self-report (scheduled visits)• 10 urine toxicology samples in total<ul style="list-style-type: none">• Applicant informed to ensure that urine sample collections not missed, particularly in a stable patient population• Few missed visits for collection of samples, but problems with analysis of some submitted urine samples

PRO-814 Trial

- **Responder:** ≤ 2 months with any evidence of illicit opioid use
- **Analysis:** Establish Non-Inferiority (NI)
 - Conceivable that a product that offers “passive compliance” may be able to demonstrate superiority, NI evaluation also considered reasonable

Efficacy evaluation strategy based in part on literature & physician survey

Efficacy Assessment

Physician Survey

	Average # times stable pt tests (+) for opioids, 6-month period (% negative)	Average opioid-negative urine tox in 6 mos, if continued on same dose (% negative next 6 mos)	Average % relapse over 6-month period if buprenorphine tx discontinued	Max reasonable change in stable pt's urine tox status, measured monthly x 6 months for pt to continue to be considered stable. (a) No change; (b) 1/6 (c) 2/6; (d) 3+/6
Mean	92%	89%	70%	14%
Median	97%	90%	75%	17%
Min – Max	75% – 100%	65% – 100%	30% – 95%	0% – 33%

Probuphine Efficacy and Safety Trial: Baseline Characteristics – PRO-814

Demographic and Baseline Characteristics – n (%)	Probuphine N=87	SL BPN N=89
Male	52 (60)	52 (58)
Race		
White	82 (94)	85 (96)
Black	3 (3)	2 (2)
Ethnicity – Non-Hispanic/Latino	84 (97)	86 (97)
Mean Age in years (SD)	38 (11)	39 (11)
Primary Opioid of Abuse – Rx Opioid	66 (76)	65 (73)
Mean Buprenorphine Treatment Episode Duration Prior to Entry in Years (Min, Max)	2.1 (0.05*, 14)	1.8 (0.2 [†] , 7.7)
Buprenorphine Treatment Episode Prior to Entry < 24 weeks (6 months)	13 (15)	15 (17)

* 0.05 years ≈ 2.6 weeks / <1 month; †0.02 ≈ 8 weeks / 2 months

Source: Adapted from Table 7, PRO-814 CSR, p. 57, and Applicant response to Agency Information Request

Probuphine Efficacy and Safety Trial: Baseline Characteristics – PRO-814

Demographic and Baseline Characteristics – n (%)	Probuphine N=87	SL BPN N=89
Mean Highest Lifetime Buprenorphine Dose (Min, Max)	14 (2, 32)	14 (4,36)
Highest Lifetime Dose (mg/day)		
8 mg	31 (36)	26 (29)
16 mg	31 (36)	41 (46)
≥24 mg	11 (13)	11 (12)
Buprenorphine Dose at Study Entry (mg/day)		
2	6 (7)	3 (3)
4	12 (14)	15 (17)
6	8 (9)	4 (5)
8	61 (70)	67 (75)

Source: Adapted from Table 9, PRO-814 CSR, pp. 59 – 60

Probuphine Efficacy and Safety Trial: Clinical Stability Checklist – PRO-814

Stability Checklist Items – %	Probuphine N=87	SL BPN N=89*
No reports of illicit opioid use past 90 days	100	100
Stable living environment	98	100
Participation in structured activity/job that contributes to community	84	89
No significant withdrawal past 90 days	99	99
Consistent participation in recommended CBT/peer support program	75	71
Consistent compliance with clinic visit requirements	97	98
Reports of low to no desire/need to use illicit opioids in past 90 days	97	96
No episodes of hospitalizations (addiction or mental health issues), emergency room visits, or crisis intervention	74	82

***Includes data from one SL BPN subject who was randomized, but never received study treatment.
Clinical Stability Checklist summary, submitted in response to Agency Information Request**

Efficacy Findings

Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting January 12, 2016

Statistical Review of Efficacy NDA 204442

Probuphine (buprenorphine hydrochloride) Implant

James Travis, PhD
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Outline

- Important Aspects of Study Design
 - Overview of Non-Inferiority
 - Responder Definition
 - Handling of Missing Data
- Efficacy Results
 - Analysis Population
 - Missing Data
 - Rescue Medication
- Conclusion

IMPORTANT ASPECTS OF STUDY DESIGN

Rationale for a Non-Inferiority Study

- This trial was intended to study the efficacy of Probuphine for patients who are currently stabilized on a lower dose of sublingual buprenorphine.
- A placebo controlled study in this population would be unethical.
- A superiority study would be infeasible because the population of interest was clinically stable and already judged to be optimally treated.
- It was agreed that a double-dummy, non-inferiority, active-controlled study comparing Probuphine with Sublingual Buprenorphine would be utilized.

Selection of the Non-Inferiority Margin

- The Applicant stated in their protocol that a margin that preserves at least 70% of the effect “should be considered clinically acceptable”.
- To obtain the non-inferiority margin the Applicant assumed that 25% of patients would maintain clinical stability if they were taken off their stable dose of 8 mg or less of sublingual buprenorphine.
- Assumed effect size 75% (difference in response rates) for sublingual buprenorphine.
- With these assumptions a margin of 20% would preserve 70% of the estimated effect size $\left(\frac{75-20}{75}\right) \approx 70\%$
- Non-inferiority can be concluded if the lower bound of the 95% confidence interval of the difference in response rate between

Responder Definition

- The Applicant defined a responder as *“a patient with no more than 2 of 6 months with any evidence of illicit opioid use.”*
- Evidence of illicit opioid use was defined as either a positive opioid urine toxicology test or self-reported illicit opioid usage.
- Subjects were to provide a total of 10 urine tests, 6 during the subject’s monthly visits and 4 randomly scheduled urine tests.
- Subjects were asked during their monthly site visits to report any opioid use during the prior month.
- Supplemental sublingual buprenorphine use was expected to be low and so was not included in the definition of a responder.

Handling of Missing Data

- The Applicant described the following procedure for imputing missing data when there were no urines were provided:
 - The rate used to impute the illicit opioid usage status would be determined by taking the mean of the intra-subject positive rate for that treatment arm.
 - In order to make this analysis more conservative the positive rate for the Probuphine arm was increased by 20% over the higher of the two rates.

Analysis Population

- The Applicant stated that they intended to use a modified Intent to Treat (mITT) population for their primary analysis.
- Two definitions provided for this population were provided:
 - All randomized subjects who received study medication (Protocol Definition)
 - All randomized subjects who received study medication **and** provided post-baseline efficacy data, i.e., a scheduled or random urine toxicology assessment (Statistical Analysis Plan Definition)
- The 2nd definition was used for the primary analysis.

EFFICACY RESULTS

Applicant's Primary Analysis Results

Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN	Superiority P-Value (2-Sided)
Applicant's Primary Analysis				
N	84	89		
Responder	81 (96%)	78 (88%)	0.088 (0.009 , 0.167)	0.03
Non-responder	3 (4%)	11 (12%)		

Analysis Population

Assigned Treatment Group	Reason for Exclusion
Probuphine	Lost to follow-up [after Day 1]
Probuphine	Lost to follow-up [after Day 1]
Probuphine	The subject was incarcerated [after Day 1]
Sublingual Buprenorphine	Requirement for general anesthesia for surgery. Subject did not receive any study medication.

Analysis Population Issues

Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN	Superiority P Value (2-Sided)
Applicant's Primary Analysis				
N	84	89		
Responder	81 (96%)	78 (88%)	0.088 (0.009 , 0.167)	0.03
Non-responder	3 (4%)	11 (12%)		
Applicant's Primary Analysis Using Protocol Definition of ITT Population				
N	87	89		
Responder	81 (93%)	78 (88%)	0.055 (-0.032 , 0.141)	0.22
Non-responder	6 (7%)	11 (12%)		

Missing Data

- There were four issues with the Applicant's original missing data strategy:
 1. Missing data were only imputed if no samples were provided for a month.
 2. Illicit opioid usage was assumed to be equally likely for missing and observed data.
 3. Subjects who provided absolutely no post-baseline efficacy assessments had a very high chance of being classified as responders.
 4. No attempt was made to account for specimens that could not be analyzed conclusively.

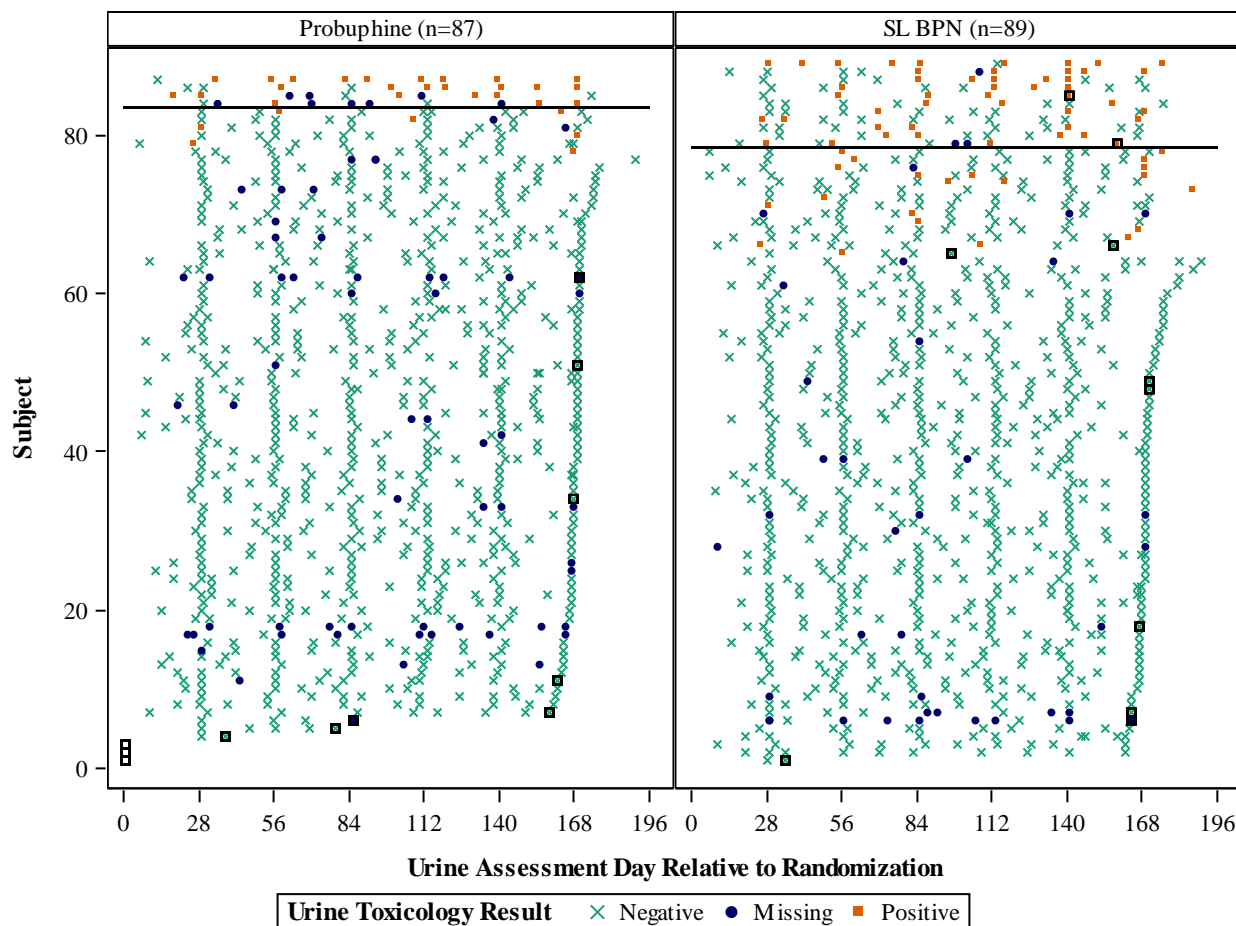
Urine Opioid Toxicology Issues

There were a number of issues with the urine toxicology results that the Applicant provided. These can be grouped into several categories as follows:

1. Norfentanyl content was unable to be determined due to “matrix problems” (66 tests).
2. Creatinine concentration and opioid/creatinine ratios were unable to be determined (17 tests).
3. Creatinine and all opioids except methadone or fentanyl were out of stability and unable to be analyzed (15 tests).

Treatment Group	Negative n (%)	Positive n (%)	Incomplete Result n (%)	Missing Sample n (%)	Total
SL BPN (n=89)	765 (86.0%)	64 (7.2%)	34 (3.8%)	27 (3.0%)	890
Probuphine (n=87)	725 (83.3%)	31 (3.6%)	60 (6.9%)	54 (6.2%)	870

Urine Toxicology Results



Black squares denote subjects who did not provide all 10 urine toxicology tests. Subjects above the line had ≥ 3 positive urine tests.

Summary of Issues

Issue	Probuphine n (%)	SL BPN n (%)	Total n (%)
N	87	89	176
No Issues	46 (53%)	49 (55%)	95 (54%)
Missing Data	31 (36%)	22 (25%)	53 (30%)
Missed Sample	11 (13%)	11 (12%)	22 (13%)
Incomplete Result	22 (25%)	16 (18%)	38 (22%)
Rescue Use	15 (17%)	13 (15%)	28 (16%)
Positive Test	10 (12%)	25 (28%)	35 (20%)

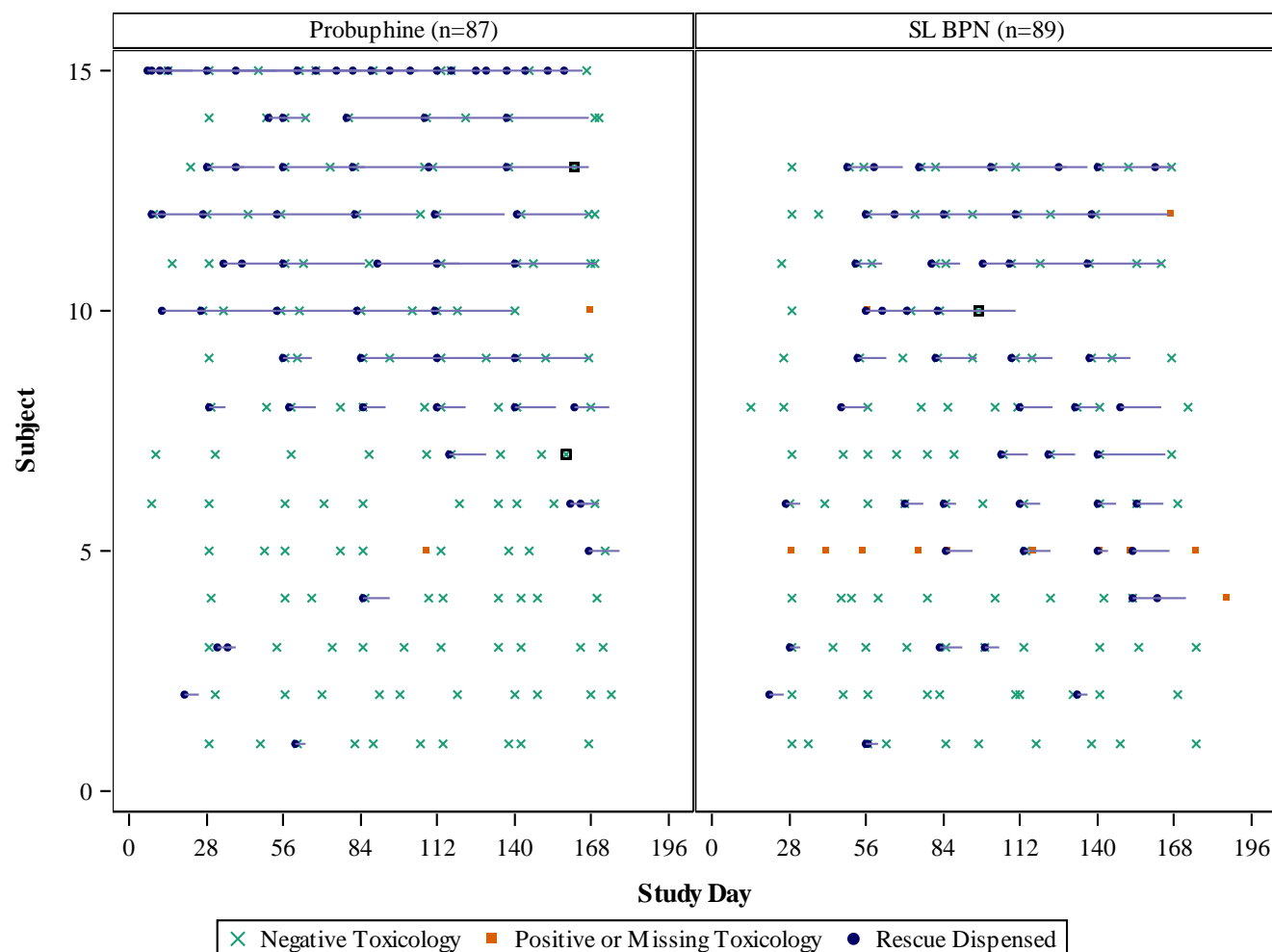
FDA's Imputation of Missing Urines

Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine - SL BPN
Missing Urine Samples Imputed as Positive			
N	87	89	
Responder	78 (90%)	76 (85%)	0.043 (- 0.055 , 0.140)
Non-responder	9 (10%)	13 (15%)	
Incomplete and Missing Urine Samples Imputed as Positive			
N	87	89	
Responder	73 (84%)	70 (79%)	0.053 (- 0.062 , 0.167)
Non-responder	14 (16%)	19 (21%)	

Supplemental Medication Use (1/2)

	Probuphine (N=84)	SL BPN (N=89)	Total (N=173)
Number of Subjects who were dispensed supplemental SL BPN	15 (17.9%)	13 (14.6%)	28 (16.2%)
Average Number of Tablets Dispensed and not Returned Per Subject Requiring Rescue	42.9	24.9	34.5

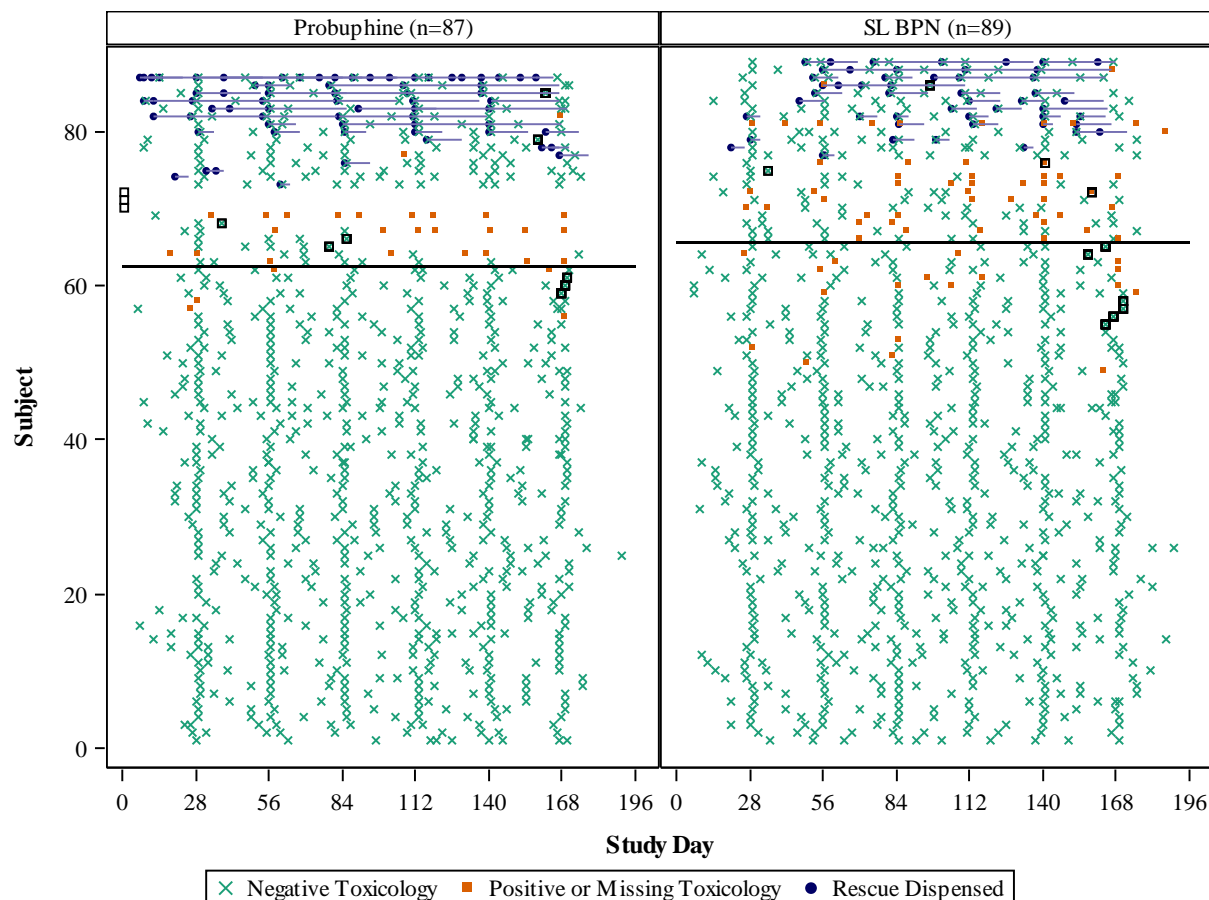
Supplemental Medication Use (2/2)



Analysis of Supplemental Medication Use

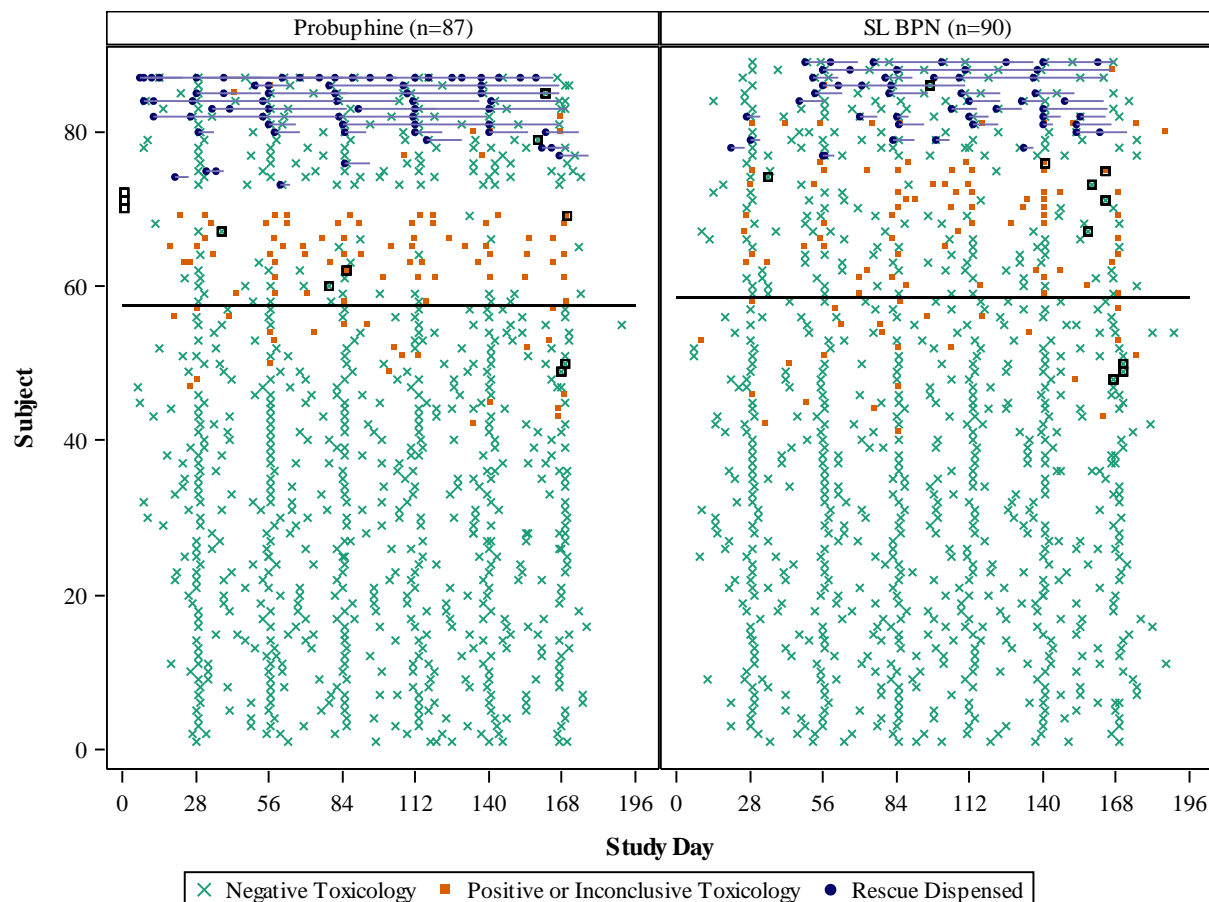
Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN
Missing Urine Samples imputed as Positive and Subjects with Supplemental Buprenorphine Use counted as Non-Responders			
N	87	89	
Responder	63 (72%)	65 (73%)	-0.006 (- 0.138 , 0.125)
Non-responder	24 (28%)	24 (27%)	
Incomplete and Missing Urine Samples as Positive and Subjects with Supplemental Buprenorphine Use counted as Non-Responders			
N	87	89	
Responder	58 (67%)	59 (66%)	0.004 (- 0.136 , 0.143)
Non-responder	29 (33%)	30 (34%)	

Missing Sample as Positive, Rescue as Non-Responder



Black squares denote subjects who did not provide all 10 urine toxicology tests. Subjects above the line were non-responders.

Inconclusive Test as Positive, Rescue as Non-Responder



Black squares denote subjects who did not provide all 10 urine toxicology tests. Subjects above the line were non-responders.

Additional Rescue Analyses

Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine - SL BPN	Superiority P Value (2-Sided)
Probuphine Subjects using Rescue as Non-Responders with Missing Samples as Positive				
N	87	89		
Responder	63 (72%)	76 (85%)	-0.130(- 0.249 , -0.011)	0.04
Non-responder	24 (28%)	13 (15%)		
Probuphine - No More Than 2 Episodes of Rescue Dispensing or Months with Illicit Opioid Use SL BPN - Normal Definition				
N	87	89		
Responder	70 (80%)	76 (85%)	-0.049 (- 0.160 , 0.062)	0.38
Non-responder	17 (20%)	13 (15%)		

CONCLUSION

Summary of Analyses

Analysis Population	Number of Allowed Positive Months	Value Imputed for Missing Data	Value Imputed for Incomplete Samples	Rescue Use Permitted		Pro. n (%)	SL BPN n (%)	Lower Bound (95% CI)
				Pro.	SL BPN			
Applicant's	2	Applicant's	Negative	Yes	Yes	81 (96%)	78 (88%)	0.009
Revised	2	Applicant's	Negative	Yes	Yes	81 (93%)	78 (88%)	-0.032
Revised	2	Positive	Negative	Yes	Yes	78 (90%)	76 (85%)	-0.055
Revised	2	Positive	Positive	Yes	Yes	73 (84%)	70 (79%)	-0.062
Revised	2	Positive	Negative	None	None	63 (72%)	65 (73%)	-0.138
Revised	2	Positive	Positive	None	None	58 (67%)	59 (66%)	-0.136
Revised	2	Positive	Negative	None	Yes	63 (72%)	76 (85%)	-0.249
Revised	2	Positive	Negative	≤ 2	Yes	70 (80%)	76 (85%)	-0.160
Revised	0	Positive	Negative	Yes	Yes	66 (76%)	57 (64%)	-0.016
Revised	0	Positive	Negative	≤ 2	≤ 2	60 (69%)	50 (56%)	-0.014
Revised	0	Positive	Negative	≤ 2	Yes	60 (69%)	57 (64%)	-0.090

PRO-814 Trial:

Summary of Challenges to Interpretation of Efficacy Data/ Defining Appropriate Population and Presenting Results

- **ITT (Intent-to-Treat) Population Definition**
 - Applicant's Definition: Randomized + received study med + provide efficacy data
 - 3 Probuphine pts received study med, provided no post-baseline efficacy data
→ omitted from ITT population
 - 2 lost to follow up; 1 incarcerated
- **Urine Toxicology Data**
 - Missed urine sample collection visits
 - Incomplete urine sample analysis and reports / sample stability
- **Rescue Buprenorphine Use**
 - Clinically stable population
 - No rescue use in prior 6 months among those receiving rescue
 - Probuphine non-titratable/fixed dosing vs. transmucosal forms
- **Study Population**
 - Buprenorphine treatment duration pre-trial
 - Transmucosal formulation used pre-trial

Summary of Analyses

Analysis Population	Number of Allowed Positive Months	Value Imputed for Missing Data	Value Imputed for Incomplete Samples	Rescue Use Permitted		Pro. n (%)	SL BPN n (%)	Lower Bound (95% CI)
				Pro.	SL BPN			
Applicant's	2	Applicant's	Negative	Yes	Yes	81 (96%)	78 (88%)	0.009
Revised	2	Applicant's	Negative	Yes	Yes	81 (93%)	78 (88%)	-0.032
Revised	2	Positive	Negative	Yes	Yes	78 (90%)	76 (85%)	-0.055
Revised	2	Positive	Positive	Yes	Yes	73 (84%)	70 (79%)	-0.062
Revised	2	Positive	Negative	None	None	63 (72%)	65 (73%)	-0.138
Revised	2	Positive	Positive	None	None	58 (67%)	59 (66%)	-0.136
Revised	2	Positive	Negative	None	Yes	63 (72%)	76 (85%)	-0.249
Revised	2	Positive	Negative	≤ 2	Yes	70 (80%)	76 (85%)	-0.160
Revised	0	Positive	Negative	Yes	Yes	66 (76%)	57 (64%)	-0.016
Revised	0	Positive	Negative	≤ 2	≤ 2	60 (69%)	50 (56%)	-0.014
Revised	0	Positive	Negative	≤ 2	Yes	60 (69%)	57 (64%)	-0.090

Summary of Analyses: Recommended Presentation of Findings

Analysis Population	Number of Allowed Positive Months	Value Imputed for Missing Data	Value Imputed for Incomplete Samples	Rescue Use Permitted		Pro. n (%)	SL BPN n (%)	Lower Bound (95% CI)
				Pro.	SL BPN			
Applicant's	2	Applicant's	Negative	Yes	Yes	81 (96%)	78 (88%)	0.009
Revised	2	Applicant's	Negative	Yes	Yes	81 (93%)	78 (88%)	-0.032
Revised	2	Positive	Negative	Yes	Yes	78 (90%)	76 (85%)	-0.055
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Revised	2	Positive	Negative	None	None	63 (72%)	65 (73%)	-0.138
Revised	2	Positive	Positive	None	None	58 (67%)	59 (66%)	-0.136
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Revised	0	Positive	Negative	≤ 2	≤ 2	60 (69%)	50 (56%)	-0.014
Revised	0	Positive	Negative	≤ 2	Yes	60 (69%)	57 (64%)	-0.090

Population	ITT population defined as randomized and received study meds
Opioid-positive months	None
Urine toxicology	missed visits positive; incompletely analyzed samples negative
Rescue	≤ 2 episodes for Probuphine; any amount for SL BPN



Safety

Probuphine Safety Database

Study	Design	Duration	Treatment Grps		
			Probuphine	Placebo	SL BPN
Phase 3, Randomized Controlled Studies					
PRO-805	PC, DB	24 wks	108	55	-
PRO-806	PC, DB, OL, AC	24 wks	114	54	119
PRO-814	AC, DB	24 wks	87		89
Phase 3, Open-Label Extension Studies					
PRO-807 (805 EXT)	OL, uncontrolled	24 wks	62	-	-
PRO-811 (806 EXT)	OL, uncontrolled	24 wks	85	-	-
Clinical Pharmacology					
TTP-400-02-01	OL, uncontrolled	24 wks	12	-	-
PRO-810	OL, cross-over	8 wks (24 wks planned)	9 (SL BPN XO)	-	-

- Safety Assessments:** Treatment-emergent adverse events (TEAEs), implant site examinations, clinical laboratory assessments (blood chemistry, hematology, and urinalysis), urine toxicology screens, ECG evaluations, vital signs

Safety Review – General Principles/Review Strategy

Drug Substance

- **Buprenorphine safety profile fairly-well characterized**
 - Probuphine Safety Database did not identify novel systemic safety findings overall

Procedural Safety

- **New implantable formulation requires minor surgery for placement of rods that are indwelling for 6 months**
 - Overall safety experience as it relates to the rod insertion and removal procedures and the indwelling rods.
 - Key findings from Human Factors evaluation

Procedural Safety Database: Phase 3 Development Program

Subjects who Underwent ≥ 1 Insertion Procedure

Trial Number	Probuphine implants	Placebo implants	Total
PRO-805	108	55	163
PRO-806	114	54	168
PRO-814	87	89	176
PRO-807	62	--	62
PRO-811	85	--	85
	456	198	654

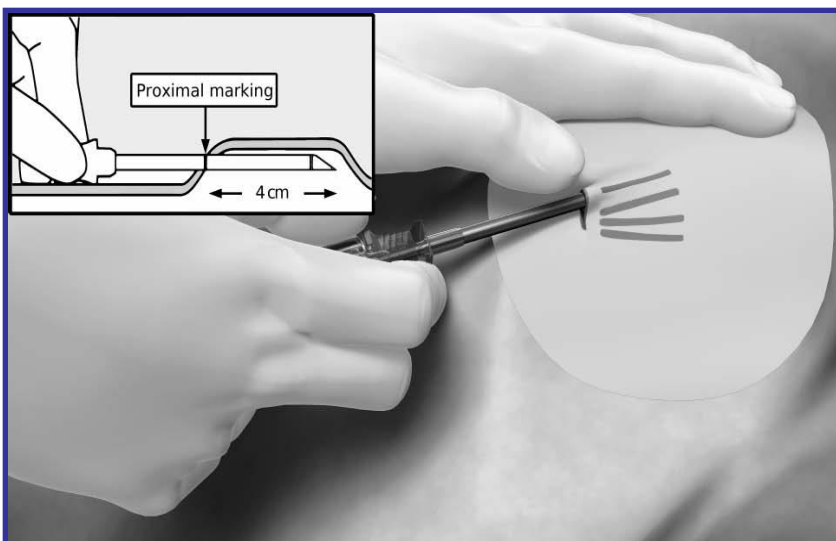
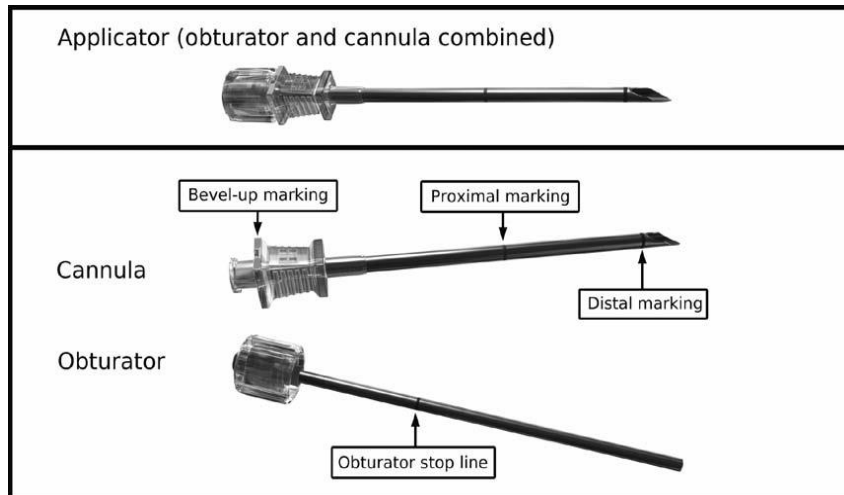
Source: Adapted from DBRUP Consult Review, December 11, 2015

Implantable Contraceptives

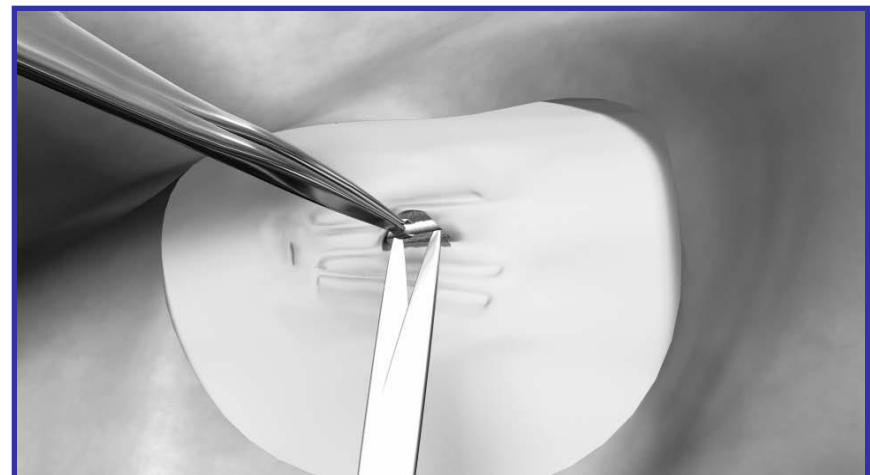
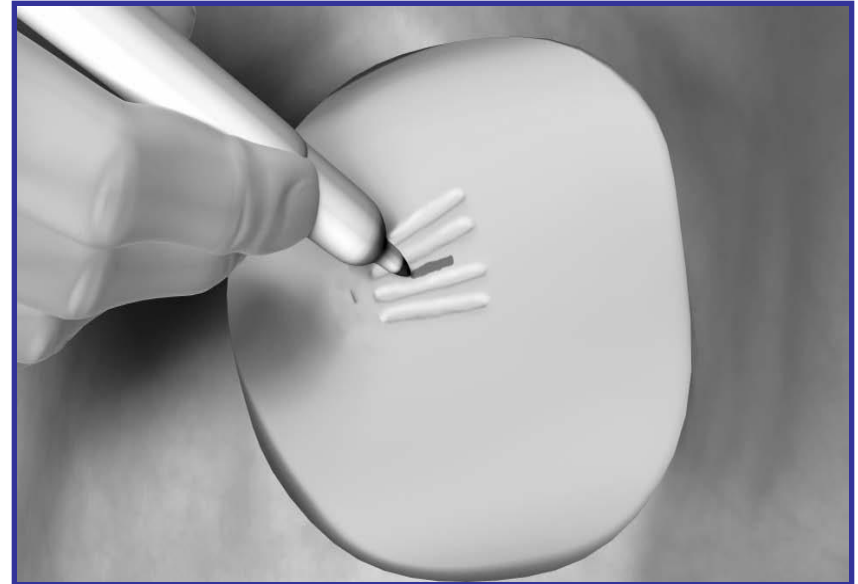
- **Norplant – 849 removals prior to approval**
- **Jadelle (Norplant-2) – >1100 removals**
- **Implanon – 842 and Nexplanon – 296**

Probuphine Administration

Insertion



Removal



Safety Summary:

Implant-Related AEs and Procedural Safety

All Implant Site Adverse Events

Phase 3 Controlled and Extension Studies – n (%)

Adverse Events in ≥ 5% of Patients who Received Probuphine or Placebo Implants

Controlled Studies		
PRO-805	PRO-806	PRO-814
87 (53)	45 (27)	32 (18)
Erythema, Itching, Pain, Edema, Bleeding Scar, Bruising	Hematoma, Pain	Pain
Open-Label Extensions		
PRO-807	PRO-811	
28 (45)	12 (14)	
Erythema, itching, pain, bleeding, edema, bruising, hemorrhage	None	

Applicator, equipment, & technique changes after 805/807 and before 806, 811, 814

Key Procedure-Related AEs: Phase 3 Controlled and Extension Studies

	Efficacy Studies			Extension Studies			
	Study 805 (N = 163)	Study 806 (N = 168)	Study 814 (N = 176)	Study 807 (N = 62)	Study 811 (N = 85)	Total # Events of Special Interest	AE incidence (% of Total # Procedures Performed, 654)
Implant expulsion ^x	5 (3.1%)	2 (1.2%)	1 (0.6%)	2 (4.8%)	0	10	1.5%
Implant site infection*	9 (5.5%)	3 (1.8%)	6 (3.4%)	4 (6.4%)	4 (4.7%)	26	4.0%
Wound complications ^{oo}	4 (2.5%)	2 (1.2%)	2 (1.1%)	1 (1.6%)	1 (1.1%)	10	1.5%
Complication of removal or requiring multiple attempts	15 (9.2%)	0	7 (4.0%)	3 (4.8%)	2 (2.3%)	27	4.1%
Bleeding**	30 (18.4%)	19 (11.3%)	1 (0.6%)	16 (25.8%)	5 (5.9%)	71	10.9%

Source: DBRUP Consult, dated December 11, 2015.

- ***Higher rates of bleeding (10.9%), complicated removals (3.2%), and implant site infections, compared with implantable contraceptives.***

Human Factors Evaluation

Key Findings

- Pork tenderloin suitable model for demonstrating technical proficiency
 - Removal procedures and potential complications not amenable to modeling
- Clinicians in the simulation component were also from specialties that involve performing procedures or surgery
 - Not generalizable to non-surgical specialties

Human Factors Study

Key Findings

- Live practicum tasks appeared appropriate
 - Most of the 15 proceduralists – physicians (8) and mid-level practitioners (7) completed – could perform tasks required to mitigate risk of infection, bleeding, and fibrous scar formation
 - Issues raised by task failures
 - Receipt of knowledge equated with ability to perform task
 - Recognize task failure → can perform task in future
 - 3 task failures relating to mitigating infection
 - Not all participants could remove all implants even in the practice session → no plan currently for how this is to be addressed in real world setting
 - 10% inserted beyond desired depth (5 – 7 mm), but less than 10 mm.

REMS

Proposed Goals

- To mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associated with the improper insertion and removal of Probuphine and the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin, through prescriber and patient education

Proposed Elements

- Training/Certification Program
 - Healthcare professionals who insert/remove product
- Restricted Distribution

Summary and Conclusions

- **Unanticipated Use of Rescue – Non-Titratable Product**
 - “Clinically Stable” patients – not included in treatment response definition
 - None who received rescue in the trial required rescue in the 6 months prior to trial entry
 - Implications for clinical practice and potential public health benefit
- **Urine Toxicology Results**
 - Analytic Difficulties vs. Missing urine samples
- **Appropriate Population for Probuphine**
 - Amount and pattern of rescue use
 - As defined by rescue use and urine toxicology results
 - Analysis (ITT) population
- **Training/Certification Procedures**
 - Removals and complicated removals
 - REMS procedural complications and abuse, misuse, and accidental overdose